



Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Indinavir (Crixivan, IDV)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Indinavir is classified as Food and Drug Administration Pregnancy Category C. Given the availability of effective alternative antiretroviral (ARV) drugs, indinavir **is not recommended** for use in pregnant women.

Animal Studies

Carcinogenicity

Indinavir is neither mutagenic nor clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred during long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.¹

Reproduction/Fertility

No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.¹

Teratogenicity/Adverse Pregnancy Outcomes

There has been no evidence of teratogenicity or treatment-related effects of indinavir on embryonic/fetal survival or fetal weights in rats, rabbits, or dogs at exposures comparable to, or slightly greater than, therapeutic human exposure. Developmental toxicity in rats, which manifested as an increase in supernumerary and cervical ribs, was observed at doses comparable to those administered to humans. No treatment-related external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure was limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to rhesus monkeys during the third trimester (at doses up to 160 mg/kg twice daily) and to neonatal rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately four-fold greater than those seen in controls receiving indinavir 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester. In rhesus monkeys, fetal plasma drug levels were approximately 1% to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing with indinavir at 40, 80, or 160 mg/kg twice daily.¹

Placental and Breast Milk Passage

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels.¹

Human Studies in Pregnancy

Pharmacokinetics

The optimal dosing regimen for use of indinavir in pregnant patients has not been established. Two studies of the pharmacokinetics (PKs) of unboosted indinavir (800 mg taken 3 times/day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum.^{2,3} Use of unboosted indinavir is not recommended in pregnant patients with HIV because of the substantially lower antepartum concentrations and the limited experience in this patient population.

Several studies have investigated the use of indinavir/ritonavir (IDV/r) during pregnancy. In an intensive PK study of 26 pregnant Thai women receiving IDV/r 400/100 mg twice daily, indinavir plasma concentrations were significantly lower during pregnancy than postpartum. The median trough indinavir concentration was 0.13 µg/mL; 24% of subjects had trough concentrations below 0.10 µg/mL, the target trough concentration used in therapeutic drug monitoring programs; and 81% of subjects had RNA viral loads <50 copies/mL at delivery.⁴ In a study of pregnant French women receiving IDV/r 400 mg/100 mg twice a day, the median

indinavir trough concentration was 0.16 µg/mL, 18% of subjects had trough concentrations below 0.12 µg/mL, and 93% of subjects had HIV RNA levels <200 copies/mL at delivery.⁵ In a small study of two patients who received IDV/r 800 mg/200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant controls.⁶ The available data are insufficient to allow for definitive dosing recommendations for use of IDV/r during pregnancy.

Placental and Breast Milk Passage

Transplacental passage of indinavir was minimal in studies of pregnant women who received unboosted indinavir. In a study of pregnant Thai women receiving IDV/r, median indinavir concentration in cord blood was 0.12 µg/mL, median maternal plasma delivery concentration was 0.96 µg/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 0.12.⁴ In one woman taking IDV/r 600 mg/200 mg twice daily, indinavir concentrations in breast milk were 90% to 540% of plasma concentrations over the first 5 days after delivery.⁷

Teratogenicity/Adverse Pregnancy Outcomes

Although the French Perinatal Cohort reported an association of head and neck birth defects with first trimester exposure to indinavir (3 defects in 350 first-trimester exposures, 0.9%), the Antiretroviral Pregnancy Registry has not observed an increase in birth defects with use of indinavir.^{8,9} Among cases of first-trimester indinavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.4% (7 of 289 births; 95% CI, 1.0% to 4.9%) compared with a total prevalence of 2.76% in the U.S. population, according to Centers for Disease Control and Prevention surveillance.⁹

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Indinavir (IDV) <i>Crixivan</i> Note: Must be combined with low-dose RTV boosting in pregnancy	<u>IDV (Crixivan)</u> Capsules: • 200 mg • 400 mg	<u>Standard Adult Dose</u> <i>Without RTV Boosting:</i> • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may be taken with skim milk or a low-fat meal. <i>With RTV Boosting:</i> • IDV 800 mg plus RTV 100 mg twice daily without regard to meals <u>PK in Pregnancy:</u> • IDV exposure markedly reduced when administered without RTV boosting during pregnancy. IDV exposure is low with IDV 400 mg/RTV 100 mg dosing during pregnancy; no PK data available on alternative boosted dosing regimens in pregnancy. <u>Dosing in Pregnancy:</u> • Use of unboosted IDV is not recommended during pregnancy.	Minimal placental transfer to fetus. ^b No evidence of human teratogenicity in cases reported to the Antiretroviral Pregnancy Registry (can rule out 2-fold increase in overall birth defects). Must be given as low-dose, RTV-boosted regimen in pregnancy. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern. Given the available alternative ARVs, IDV is not recommended for treatment of pregnant women in the United States.

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 10](#)).

^b Placental transfer categories are determined by the mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; IDV = indinavir; PK = pharmacokinetic; RTV = ritonavir

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